REMARKS

Claims 1-3 and 5-67 are pending in the application.

Claims 7-13, 17-40, and 42-67 have been withdrawn from consideration as being drawn to non-elected subject matter.

Claim 4 has been cancelled without prejudice

Claims 1-3, 5, 14, 15, and 41 have been amended.

I. Amended Claims 1-3, 4, 14, 15, and 41

Claim 1 has been amended to refer to specific preferred active and inactive Raf proteins, presented in two separate Markush groups, and to indicate that the pharmaceutical composition is administered to a patient for treating diseases by modulating angiogenesis. Support for this amendment is found in the specification at page 4, lines 1-18, and on page 37, line 13 through page 38, line 18, and in the original claims as filed.

Claim 2 has been amended to conform the language of the claim to amended claim 1, from which is depends.

Claim 3 has been amended to clarify the term wild type Raf protein as referring to c-Raf having SEQ ID NO: 2). Support for this amendment is found in the specification on page 37, line 16.

Claim 5 has been amended to add the sequence identifier "SEQ ID NO: 7" after "Raf-caax." Support for this amendment is found in the specification on page 50, lines 3-4.

Claim 14 has been amended to be consistent with claim 1 in reciting "is administered to a patient" in place of the phase "said administering," which lacked antecedent basis in the original claims.

Claim 15 has been amended to be consistent with claim 1 in reciting "is administered to a patient" in place of the phase "said administering," which lacked antecedent basis in the original claims.

Claim 41 has been amended to recite a Markush listing of active Raf proteins in place of the phrase "a Raf protein, said Raf protein having kinase activity." Support for this amendment is found page 4, lines 11-18, and on page 37, line 13 through page 38, line 2.

No new matter is added by any of the aforementioned amendments.

II. Amendment to the Title

The specification was objected to under 35 U.S.C. §132 because the amendment to the title filed on June 14, 2001 introduced new matter. The specification has been amended to restore the title to its original text.

III. Claims 1-3, 5, 6, and 14-16 State Proper Markush Groups Under 37 C.F.R. 1.75(d)(1)

Claims 1, and claims 2-6 and 14-16 depending therefrom were objected to under 37 C.F.R. 1.75(d)(1) as being in improper form because claim 1 stated an improper Markush group. The Office Action, at page 4, states that the listing of a protein and an oligonucleotide in the same Markush group in claim 1 is improper because the two members of the group do not share a common utility or a common structural feature. Claim 1 has been amended to limit the claim to proteins. Applicant requests that this objection be withdrawn as moot.

IV. Claims 1-3, 5, 6, 14-16 and 41 are not indefinite

Claims 1-3, 5, 6, 14-16 and 41 stand rejected under the second paragraph of 35 U.S.C. §112 as being indefinite for reciting the term "Raf protein." According to the Office Action, the term Raf protein is indefinite because the specification does not clearly define the metes and bounds of "Raf." Applicant respectfully submits that the term Raf is well known and understood in the art; however, in the interest of furthering prosecution of this Application, claim 1 has been amended to list specific preferred Raf proteins. Support for this amendment is found in the specification at page 4, lines 1-18, and on page 37, line 13 through page 38, line 18. In view of this amendment, the present claims are deemed in compliance with the second paragraph of 35 U.S.C. §112.

V. Claim 41 is Not Anticipated by Skopinska-Rozewska *et al.*

Claim 41 stands rejected under 35 U.S.C. §102(a) as being anticipated by Skopinska-Rozewska *et al.* This rejection is unwarranted.

As noted on page 7 of the Office Action, the applied reference teaches transfection of urothelial cells (HCV-29) with a polynucleotide encoding v-Raf. It is further asserted that v-Raf transfected cells represent a pharmaceutical composition. Claim 41, as currently amended, is directed to a pharmaceutical composition for stimulating angiogenesis

comprising an *isolated active Raf protein* and a pharmaceutically acceptable carrier or excipient. V-Raf transfected cells are not isolated Raf proteins. Furthermore, Skopinska-Rozewska *et al.* do not teach or suggest the use of these cells as a pharmaceutical composition. Additionally, there is no teaching or suggestion in the reference to use an isolated active Raf protein in a pharmaceutically acceptable carrier for stimulating angiogenesis. Rather, the article teaches the use of theobromine and theophylline to *suppress* cutaneous neovascularization, i.e. inhibit angiogenesis. See Skopinska-Rozewska *et al.*, page 649, Abstract. Thus, the reference teaches away from the claimed invention which is directed to *stimulating* angiogenesis. The applied reference does not teach or suggest all of the limitations of the claim, and teaches away from the claimed invention. Therefore, claim 41 is patentable over Skopinska-Rozewska *et al.*

VI. Claim 41 is Not Anticipated by Zhou *et al.*

Claim 41 stands rejected under 35 U.S.C. §102(b) as being anticipated by Zhou *et al.* This rejection is also unwarranted.

Zhou *et al.* teach angiogenesis induced by transfecting human breast carcinoma cells with a gene (i.e. an oligonucleotide) encoding Raf-caax. Claim 41 is directed to a pharmaceutical composition comprising a protein, not an oligonucleotide. As pointed out on page 5 of the Office Action, "a protein and an oligonucleotide are structurally and functionally different and have different utilities." Zhou *et al.* do not teach or suggest the use of an isolated active Raf protein to stimulate angiogenesis. There is no teaching in the reference to suggest that oligonucleotides for transfecting cells with a Raf gene is the same invention as isolated Raf proteins for stimulating angiogenesis in a target tissue, as presently claimed. Since Zhou *et al.* do not teach or suggest the same invention as Claim 41, this claim cannot be anticipated by the applied reference.

VII. Claims 1-3, 5, 6, 14-16 and 41 are Not Obvious over Zhou *et al.*

Claims 1-3, 5, 6, 14-16 and 41 stand rejected under 35 U.S.C. §103(a) as being obvious over Zhou *et al.* In order to establish a *prima facie* case for obviousness, all claim limitations must be taught or suggested by the prior art. *In re Royka*, 180 USPQ 580 (CCPA 1974). Additionally, "All words in a claim must be considered in judging the patentability of

that claim against the prior art." *In re Wilson*, 165 USPQ 494, 496 (CCPA 1970). That is not the case here.

Contrary to the assertion on page 8 of the Office Action, Zhou *et al.* do not teach the induction of angiogenesis by a Raf fusion protein. Rather, this reference teaches the induction of angiogenesis by transfecting a cell with a gene encoding a Raf-fusion protein. There is no teaching or suggestion in the reference that administering an isolated active Raf protein to a patient will induce angiogenesis. Zhou *et al.* is directed to activation of Tissue-Factor (TF) gene expression, and not to stimulation of angiogenesis *per se*. According to the reference, "TF is a cell-surface glycoprotein responsible for initiating the extrinsic pathway of coagulation." Zhou *et al.*, page 234, column 1, first paragraph of the introduction. "TF has also been implicated in metastasis." *Id.* at page 234, column 1, third paragraph of the introduction. Thus, Zhou *et al.* teach that transfection of tumor cells with Raf-caax produces the undesirable result of stimulating a process (TF expression) that leads to metastasis. Furthermore, the reference teaches that little is known about genes activated by signaling pathways, such as the Raf-ERK pathway. *Id.* at page 243, column 1, last paragraph before the acknowledgments. Thus, at best, Zhou *et al.* would have presented to one of ordinary skill in the art at the time the application was filed nothing more than an invitation to experiment without any reasonable expectation of success. That is not the standard for obviousness. All of the presently pending claims are directed to articles of manufacture or pharmaceutical compositions comprising isolated Raf proteins, which are not taught or suggested by the applied reference. Therefore, Claims 1-3, 5, 6, 14-16 and 41 are not obvious over Zhou *et al.* Accordingly this ground for rejection should be withdrawn.

VIII. Claims 1-3, 5, 6, 14-16 and 41 are Not Obvious Over Monia *et al.*

Claims 1-3, 5, 6, 14-16 and 41 stand rejected under 35 U.S.C. §103(a) as being obvious over Monia *et al.* U.S. Patent No. 5,952,229. Monia *et al.* is directed to antisense oligonucleotide modulation of Raf gene expression. Specifically, Monia *et al.* teaches that antisense oligonucleotides are useful in pharmaceutical compositions to inhibit expression of Raf genes. Inhibiting expression of Raf genes leads to inhibition of hyperproliferation of cells and provides methods of treating abnormal proliferative conditions. See U.S. 5,952,229, Abstract. The present claims are all directed to articles of manufacture and pharmaceutical compositions

comprising isolated Raf proteins, and not oligonucleotides as taught by Monia *et al.* Monia *et al.* teach compositions and methods of treatment involving administering oligonucleotides, which are functionally and structurally distinct from the presently claimed protein compositions. The teachings of Monia *et al.* are inapposite to the presently claimed invention.

Furthermore, claims 2,3, 5, 6, 14-16 and 41 are exclusively directed to articles of manufacture and compositions useful for *stimulating* angiogenesis, whereas Monia *et al.* is directed to methods of inhibiting Raf gene expression, which would *inhibit* angiogenesis. Therefore, Monia *et al.* teach away from the invention claimed in claims 2,3, 5, 6, 14-16 and 41.

None of the present claims are rendered obvious by Monia *et al.* This ground for rejection should also be withdrawn.

IX. Conclusion

Claims 1-3, 5, 6, 14-16, and 41 meet all of the requirements of 35 U.S.C. §112 and are patentable over the applied art. Reconsideration and early passing of this application to issue is earnestly solicited.

Respectfully submitted,

Dated: 24 April 2003

By /Talivaldis Cepuritis/
Talivaldis Cepuritis (Reg. No. 20,818)

OLSON & HIERL, LTD.
20 North Wacker Drive
36th Floor
Chicago, Illinois 60606
(312) 580-1180